Remarks

Claims 1 and 10 have been amended to define the combination and package as reducing bone loss caused by the treatment with an aromatase inhibitor of a disease or condition which responds to aromatase inhibition. Support for the newly amended claims can be found throughout the specification. More specifically, support can be found in Example 6 starting on page 50. The Examples describes the administration of zoledronic acid to protect against cancellous bone loss, cortical thinning and reduction of bone loss by daily oral administration of letrozole.

35 U.S.C. 112, first paragraph paragraph rejection

Claims 1 and 10 were rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for the prevention of bone loss as recited in the claims. Claims 1 and 10 have been amended to remove the term "prevention of bone loss" and therefore, Applicants respectfully request this rejection be withdrawn from consideration.

35 U.S.C. 103(a) Rejection

Claims 1, 18, 19, 22-24 were rejected under 35 U.S.C. 103(a) as being unpatentable over Freyer et al. in view of Reid (N. Engl. J. Med., 2002) and Iqbal (Expert Opin. Pharmacother.). The Examiner argues it would have been obvious to one of ordinary skill in the art at the time of the invention to have employed the administration of an aromatase inhibitor and a bisphosphonate as taught by Freyer, using specifically zoledronic acid as the bisphosphonate and letrozole as the aromatase inhibitor. Claim 10 was rejected under 35 U.S.C. 103(a) as being unpatentable over Freyer et al. in view of Reid (N. Engl. J. Med., 2002) and Iqbal (Expert Opin. Pharmacother.) as applied to claims 1, 18, 19, 22-24 above in further view of Remington's: The Science and Practice of Pharmacy, Nineteenth Edition, Vol. , 1985, page 806. The Examiner argues that it would have been obvious to one of ordinary skill in the art to have combined the aromatase inhibitor and bisphosphonate as taught by Freyer, Reid and Iqbal and included the medication as package with instructions. Applicants respectfully disagree.

Similar obviousness rejections were made by the Examiner in the previous Official Action. However, the Examiner has not commented on the unexpected results described in Example 6 of the specification. Example 6, starting on page 50 of the specification describes the effectiveness of intravenous administration of zoledronic acid in preventing the bone loss and reduction of mechanical properties induced by aromatase inhibition or surgical ovariectomy in rats. The results showed a single iv injection of 0.8 µg/kg zoledronic acid delayed bone loss significantly for 24 weeks in patients treated with letrozole with the highest dose being full protective over the entire 24-week duration of the study, page 51 lines 6-10 of the specification. The findings of this study were summarized on page 52 of the specification:

> Discussion: Our data indicates for the first time that in rats, Zol dose-dependently protects against cancellous bone loss, corical thinning and reduction of bone strength induced by daily oral letrazole, at a dose of 20μg/kg, fully protects against letrozole induced bone loss for at least 24 weeks.

Applicants argue none of the cited references described the unexpected results found by combining letrozole with zoledronic acid. Objective evidence or secondary considerations such as unexpected results, commercial success, long-felt need, failure of others, copying by others, licensing, and skepticism of experts are relevant to the issue of obviousness and must be considered in every case in which they are present. When evidence of any of these secondary considerations is submitted, the examiner must evaluate the evidence. *Stratoflex, Inc. v. Aeroquip Corp.,* 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987).

Since all of the references cited published before the Food and Drug Administration approved zoledronic acid, under the trademark ZOMETA, Applicants maintain that, at the time of the publication of Freyer et al. and Iqbal et al. it would not have been common practice or even general knowledge among one of ordinary skill in the art to combine the methods of treatment as taught by Freyer et al. and Iqbal to arrive at the inventions recited in the claims.

Reid does not correct the deficiencies of Freyer et al. and Iqbal et al.. Reid does not teach or suggest combining zoledronic acid with an aromatase inhibitor to treat bone loss associated with the administration of an aromatase inhibitor. As stated above, Example 6 of the specification describes the unexpected result of zoledronic acid protecting against cancellous bone loss, corical thinning and reduction of bone strength induced by daily oral administration of letrozole.

The newly amended claims are non-obvious over the cited references because it would not have been obvious to one of ordinary skill in the art at the time of the invention to have employed the administration of an aromatase inhibitor and a bisphosphonate as taught by Freyer, using specifically zoledronic acid as the bisphosphonate and letrozole as the aromatase inhibitor. Applicants respectfully request the obviousness rejection be withdrawn from consideration. Entry of this Response is respectfully requested.

Respectfully submitted,

Lydia M. McNally

Novartis Pharmaceuticals Corp.
Patents Pharma
One Health Plaza, Building 104
East Hanover, NJ 07936-1080
(862) 778-7898

Lydia T. McNally
Attorney for Applicants
Reg. No. 36,214

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